Journal of Fluorine Chemistry 132 (2011) 945–950

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

# Mechanistic study of multi-step nucleophilic substitution for trifluoromethylated styrenes

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ARTICLE INFO

*Article history:*
Received 16 June 2011
Received in revised form 16 July 2011
Accepted 18 July 2011
Available online 23 July 2011

*Keywords:*
Reaction mechanisms
β-Halo-β-trifluoromethylstyrenes
Amines
Domino reactions

ABSTRACT

The key steps of the reactions of nitrogen nucleophiles with β-halogen-β-trifluoromethylstyrenes have been studied by $^{19}F$ and $^{1}H$ NMR monitoring and quantum-chemical calculations. In contrast to the mechanism proposed earlier for nucleophilic vinylic substitution of captodative carbonyl-bearing haloalkenes, this reaction proceeds *via* either E–Ad or Ad–E sequence depending on the nature of aromatic substituents of the parent styrenes.



## 1. Introduction

Nucleophilic vinylic substitution ($S_NVin$) is a general type of reactions for the synthesis of variety of unsaturated heteroatomic systems including biologically important compounds [1]. It is well known that the substitution of inactivated vinyl halides is a very difficult process. But it is facilitated if an electron-withdrawing group is present in the β-(push–pull olefins) or α-position (captodative olefins) to the leaving group. It should be noted, however, that for both cases the reaction does not occur as a direct nucleophilic substitution of the halogen atom at the double bond. Thus, among the different approaches to the captodative aminoalkenes, the nucleophilic vinylic substitution of the halide ion by the nitrogen nucleophile seems to be the more attractive method for its simplicity [2]. Previously this methodology was successfully applied to the synthesis of captodative enamines bearing carbonyl, formyl, alkoxycarbonyl or cyano functionalities [2,3].

The result of $S_NVin$ reaction is the replacement of an appropriate leaving group (for example, halogen) by various nucleophiles. In spite of the transformation looks simple by now, many mechanistic variants of $S_NVin$ processes have been proposed depending on the structure of initial substrate or nucleophile, nature of the leaving group, experimental conditions [1]. The most versatile among β-activated (push–pull olefins) includes two-step addition–elimination sequence. However, some vinylic systems can undergo a much more complicated substitution. Thus, the formation of captodative carbonyl-bearing aminoalkenes is a multi step (Ad-$S_N$2-E) process and occurs *via* nucleophilic addition of one equivalent of amine to the activated double bond of the initial substrate, followed by classical substitution of the halogen atom at the $sp^3$-carbon center by second amine equivalent and finally an elimination of β-amine to produce captodative enamine derivative (Scheme 1) [2a].

Our interest in the chemistry of captodative systems, in particular aminoalkenes, led us to research of the new type of captodative enamines bearing perfluoroalkyl group as an acceptor [4]. The fluorine-bearing enamines are the target compounds for chemical, medicinal and agricultural research. At the beginning of 21st century the interest for both captodative and push–pull trifluoromethylated enamines has grown due to their remarkable and specific properties as well as to their application as potential precursors of various fluorine-containing biologically active acyclic and heterocyclic compounds [5]. In contrast to early studied aminoalkenes, these derivatives have an electron-withdrawing group which is not capable to π,π-conjugation with the double bond. Recently, we have found that the unusual reactions of

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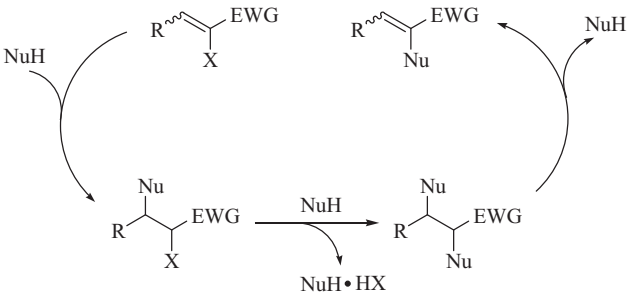
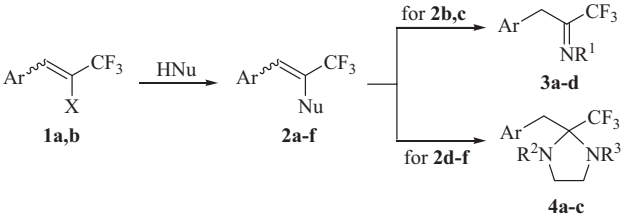
doi:10.1016/j.jfluchem.2011.07.015



**Scheme 1.** The general scheme of formation of captodative carbonyl-bearing aminoalkenes. EWG = CHO, C(O)R, COOR, CN.



**Scheme 3.** The reactions of N-nucleophiles with EWG-substituted styrenes. **1**–**4**: Ar = 4-$O_2NC_6H_4$; **1**: X = Cl (**a**), X = F (**b**); **2**: Nu = $N(CH_2)_4$ (**a**), NHCy (**b**), $NHPr^i$ (**c**), $NH(CH_2)_2NH_2$ (**d**), $NH(CH_2)_2NHMe$ (**e**), $NMe(CH_2)_2NHMe$ (**f**); **3**: $NR_1$ = NCy (**a**), $NHPr^i$ (**b**), $N(CH_2)_2NH_2$ (**c**), $N(CH_2)_2NHMe$ (**d**); and **4**: $R_2 = R_3 = H$ (**a**), R2 = H, $R_3$ = Me (**b**), $R_2 = R_3$ = Me (**c**).

trifluoromethylated bromo- and chlorostyrenes with nitrogen nucleophiles are synthetically valuable and mechanistically intriguing processes leading to either target enamines or surprising products of $CF_3$ group cleavage [6–8]. We have shown that the direction of transformations depends dramatically on the nature of aromatic substituent of initial substrate: styrenes bearing an electron-withdrawing group are converted into trifluoromethylated enamines (secondary amines) and/or azomethines (primary amines) or heterocycles (binucleophiles) while their analogs bearing electron-donor group in benzene ring give unexpected products of nucleophilic C–F bond cleavage (primary or secondary amines) or fragmentation (binucleophiles) (Scheme 2).

There still remains a question: what are the key steps of the intricate processes and how the nature of the aromatic substituent influences the reaction mechanism and direction of the transformation? A clear understanding of the mechanism of these transformations is essential for their confident realization. In previous papers [6–8] we have proposed a hypothetical scheme of the synthesis of the major reaction products. Our recent experimental and theoretical research has been devoted to its clarification and corroboration. Here, we report the results of the comprehensive study of the mechanism of these non-trivial transformations.

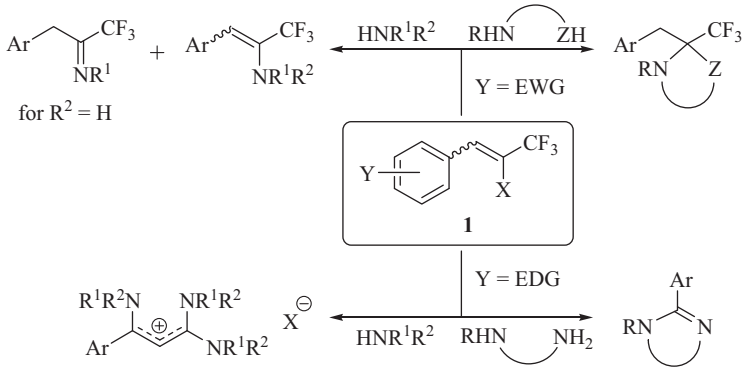
## 2. Results and discussion

### 2.1. Styrenes bearing electron-withdrawing substituent

In a first set of experiments we have monitored by $^{19}F$ and $^1H$ NMR spectroscopy the reactions of amines with styrenes bearing an electron-withdrawing substituent in the benzene ring (Scheme 3). The treatment of styrene **1a** with a six molar excess of pyrrolidine in methanol at room temperature results in the rapid disappearance of the initial substrate $^{19}F$ signals (−69.8 (*Z*-isomer) and −62.4 ppm (*E*-isomer)) and subsequent appearance of two new resonances (−65.5 and −59.3 ppm) which are observed approximately a minute after mixing (see Supporting Information, Section 1.1). These signals were assigned by NOESY experiments to the *Z*- and *E*-isomers of the enamine **2a**. Both the geometric isomers of **1a** reacted simultaneously and the target product **2a** was formed as a (75:25) mixture of *Z*- and *E*-isomers. An important observation was made upon the monitoring: the *Z*/*E* isomer ratio of the product remained constant during the course of the reaction. The kinetic of the reaction obtained by $^{19}F$ NMR reveals simultaneous disappearance of *E*- and *Z*-isomers of **1a** and formation of **2a** as the mixture of *E*- and *Z*-isomers (Fig. 1). Any other signals were not observed during all time of the monitoring. Similar to secondary amines, isopropyl- or cyclohexylamine react with styrene **1a** very easily at room temperature. But in these cases the enamines **2b**,**c** are formed along with their tautomers **3a**,**b** (see Supporting Information, Section 1.2).

A similar experiment was performed with styrene **1b** bearing fluorine as a leaving group. When styrene **1b** was treated with pyrrolidine in methanol, only signals of enamine **2a** as a reaction product together with the singlet of anion $F^-$ (ca. −143 ppm) were observed. Starting from 10:1 mixture of *Z*/*E*-**1b** the substitution of the fluorine atom afforded the enamine **2a** as an equimolar mixture of geometric isomers. The $^{19}F$ NMR monitoring in MeOH at room temperature has clearly indicated that the reaction results in the formation of target product **2a** only which was isolated by column chromatography in 96% yield.

Next we have monitored the reaction of styrenes **1a**,**b** with ethylenediamine and its N-methyl- or N,N′-dimethylsubstituted derivatives. When styrene **1b** was treated with ethylenediamine, the spectrum taken after 30 min shows singlets of **1b** along with low intensity resonances of enamine *E*,*Z*-**2d** (−63.1 and −69.2 ppm) and its azomethine tautomer *E*,*Z*-**3c** (−72.4 and −74.1 ppm). The intensities of these signals were increased for the initial 2 h and after that they were decreased gradually during all time of the monitoring. Simultaneously, the intensity of the singlet of the heterocycle **4a** (−80.5 ppm) was increased and its content reached 85% of the reaction mixture after 16 h. Because the



**Scheme 2.** The reactivity of trifluoromethylated styrenes.

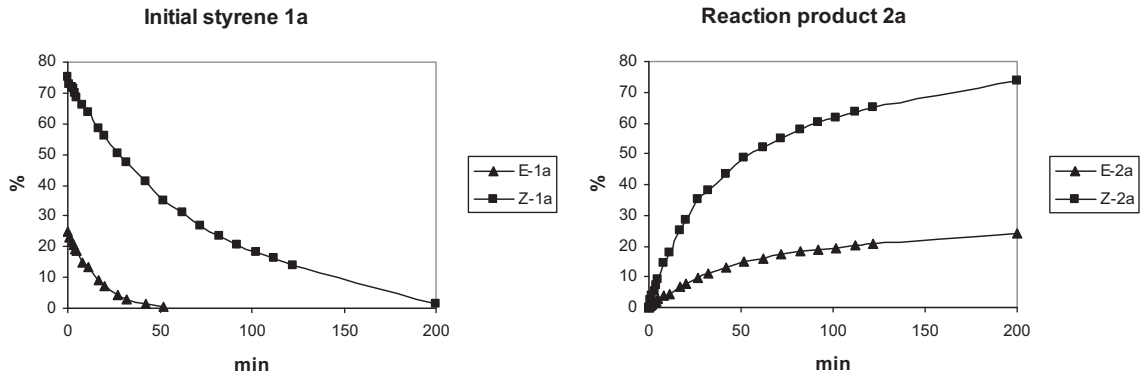



**Fig. 1.** The integrated peak intensity in $^{19}F$ NMR spectra as a function of time for the reaction of styrene **1a** with pyrrolidine.

intensities of the signals of the intermediates **2d** and **3c** were low during the course of the reaction we can conclude that both the enamine or azomethine formation and their cyclization occurs simultaneously with approximately equal reaction rate. Similar results were observed for the reaction of **1a**,**b** with N-methyl- and N,N′-dimethylethylenediamine (see Supporting Information, Section 1.3).

It should be noted that the reaction of **1b** with N,N′-dimethylethylenediamine proceeds more slowly. Moreover, after 1.5 h the $^{19}F$ NMR spectra of the reaction mixture with N-methylethylenediamine indicated the formation of two pairs of intermediates – azomethines **3d** and enamines **2e** (*Z*/*E*-isomers mixtures). This means that the reaction proceeds highly chemoselectively and the primary amino group reacts more easily with alkenes **1**. Probably this selectivity can be explained by sterical control of the reaction with bulky $CF_3$ group.

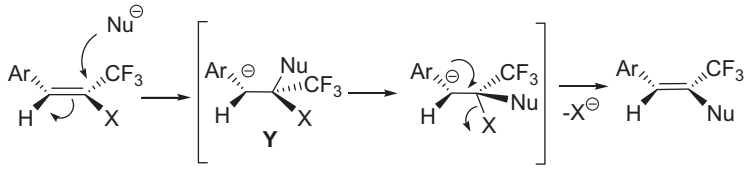
The results obtained can be explained in terms of multi-step process, which includes the initial formation of the *ipso*-substitution products **2a**–**f**. Taking into account a rich array of the possible mechanisms of nucleophilic vinylic substitution [1b] we should suggest that aminostyrenes **2a**–**f** are formed *via* addition–elimination (Ad–E) sequence. Although in all these cases any intermediate of the transformations of halostyrenes **1a**,**b** into substitution products **2a**–**f** was not observed and the general mechanism is still a matter of debate, there are significant arguments for the corroboration of the Ad–E pathway.

Strong confirmation of Ad–E mechanism for the **1a** is obtained by comparison of the vicinal coupling constants between $CF_3$ carbon atom and olefinic proton ($^3J_{H,CF}$ = 5.5 Hz for both compounds **1a** and **2a**). Their value let us to conclude that the major isomer of enamine **2a** and initial styrene **1a** have the same geometry. As a rule Ad–E mechanism gave the retention of the configuration of the double bond of alkene [1c]. The first step of the sequence is the perpendicular attack of amine on the double bond to form carbanion **Y**. After 60° turn the conformation for anti-elimination is formed. Finally it gives the alkene with retention of configuration (Scheme 4).

It could be predicted that if the reaction of styrenes **1a**,**b** with nitrogen nucleophiles proceeds according to Ad–E scheme, its rate should be much higher for fluorine-bearing styrene **1b** because the strongly electron-withdrawing fluorine increases the electrophilicity of the attacked carbon atom. To study the effect of leaving group the equimolar mixture of styrenes **1a** and **1b** in methanol was treated with 15-fold excess of pyrrolidine at room temperature and next was monitored by $^{19}F$ NMR spectroscopy. The reaction of **1b** went to completion in 5 h and the target enamine **2a** was formed as a (1:1) mixture of *Z*/*E*-isomers. In contrast, even after an extended reaction time up to 10 h the large amount (20%) of styrene **1a** was remained. No other signals were detected during the course of the reaction. Therefore, the styrene **1b** has demonstrated much higher activity in comparison with its analog **1a** in the $S_NVin$ reaction confirming again Ad–E mechanism.

It should be noted that the stereochemical result of the reaction of **1b** is not so strict compared to **1a**. However, the formation 1/1 diastereomers mixture in the case of fluorine as a nucleophuge can be again rationalized in the frames of Ad–E mechanism. Fluorine is a bad leaving group, from the other hand it stabilizes significantly the carbanion **Y**. As a result **Y** (*X* = *F*) has longer life time and can be protonated and further dehydrohalogenated to give final mixture of Z/E isomers **2a** in 1/1 ratio.

The preference only of the α-addition of amines to the double bond of the starting styrenes **1a**,**b** can be easily explained by means of the electronic effects. 4-Nitrophenyl and trifluoromethyl groups have similar values of inductive constants ($\sigma_I$) and electronegativity ($\chi$) ($\sigma_I$ = 0.26–0.34 and $\chi$ = 2.98 for 4-$NO_2C_6H_4$; $\sigma_I$ = 0.32–0.41 and $\chi$ = 2.32 for $CF_3$ [9]. At the same time 4-nitrophenyl group possess very strong negative mesomeric effect, which should lead to the appearance of some positive charge at the $C_\alpha$ olefinic carbon atom. As a result, the nucleophilic attack is regioselective and occurs at the α-position of the double bond to the electron-withdrawing function [10]. Such polarization of the double bond can be also confirmed by referring to the $^{13}C$ NMR data. Thus, it is well known that the difference in the chemical shifts of two adjacent carbon atoms can be used for estimation of the degree of double bond polarization [11]. According to $^{13}C$ NMR spectra, the differences $\delta(C_\alpha) - \delta(C_\beta)$ reach 17 ppm for **1a**,**b**. Therefore, the nucleophilic attack on the $C_\alpha$ olefinic carbon atom of starting materials **1a**,**b** is preferable and styrene **1b** should be more active




**Scheme 4.** Mechanism of the reaction of EWG-substituted styrenes with N-nucleophiles.

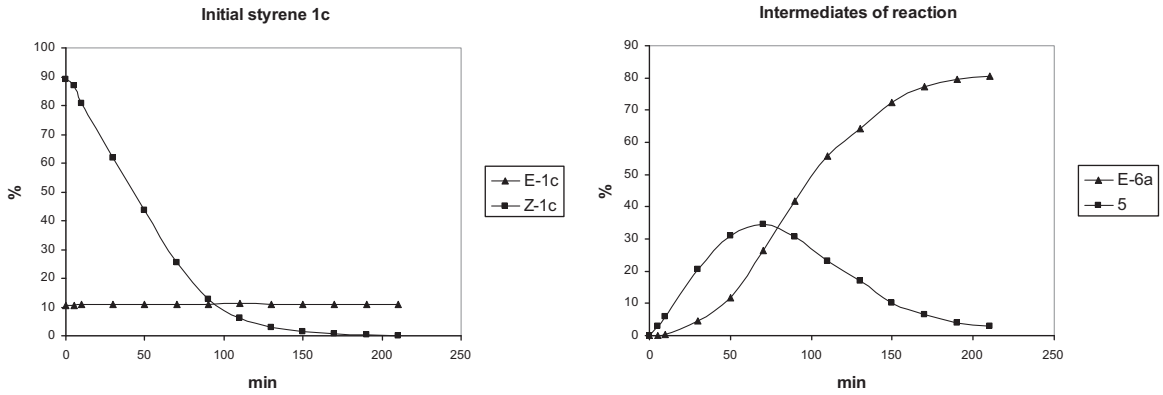


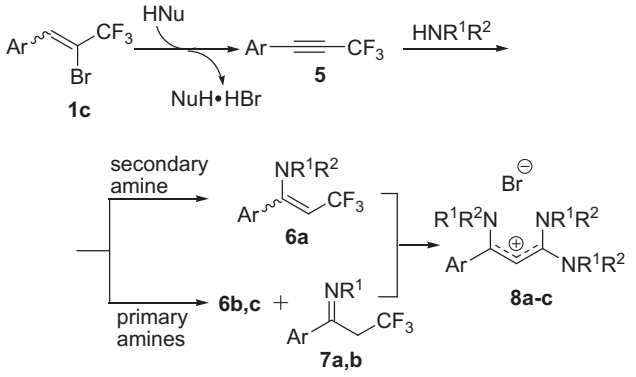

**Fig. 2.** The integrated peak intensity in $^{19}F$ NMR spectra as a function of time for the reaction of styrene **1c** with pyrrolidine.

in the nucleophilic addition reaction. Moreover, the substitution proceeds *via* carbanion in which the negative charge is effectively stabilized by the aryl group bearing an electron-withdrawing substituent. Since the last step of the sequence (halide ion elimination) is much faster than the amine addition, the proposed intermediate could not be detected by $^{19}F$ NMR.

We also performed quantum-chemical calculations at the MP2/6-311 + G(d,p) level to clarify the mechanism for the regioselectivity of the nucleophilic attack on the double bond of the styrenes **1a**,**b**. The styrenes bearing electron-withdrawing ($NO_2$) aromatic substituent and either fluorine or chlorine at the olefinic carbon atom were chosen as a model compounds in the reaction with methylamine. In the case of styrene **1a** bearing chlorine as a leaving group the formation of α-adduct is preferred over the β-one by 5.9 kcal/mol, whereas for the fluorinated analog **1b** this value is 9.2 kcal/mol.

### 2.2. Styrenes bearing electron-donor substituent

Next we tested the behavior of styrene **1c** bearing an electron-donor substituent in the aromatic ring. Accordingly NMR data the treatment of **1c** with 10–15-fold excess of pyrrolidine results in its rapid dehydrobromination and formation of acetylene **5** [12]. It is important to note that in contrast to styrenes **1a**,**b**, *Z*- and *E*-isomers of **1c** have different activity. According to the $^{19}F$ NMR spectra the *E*-**1c** does not react at all with pyrrolidine while styrene *Z*-**1c** disappeared completely for 3 h at room temperature (Fig. 2, Scheme 5). This result can be explained in terms of preferable anti-elimination of HBr to form acetylene **5** only from *Z*-**1c**.



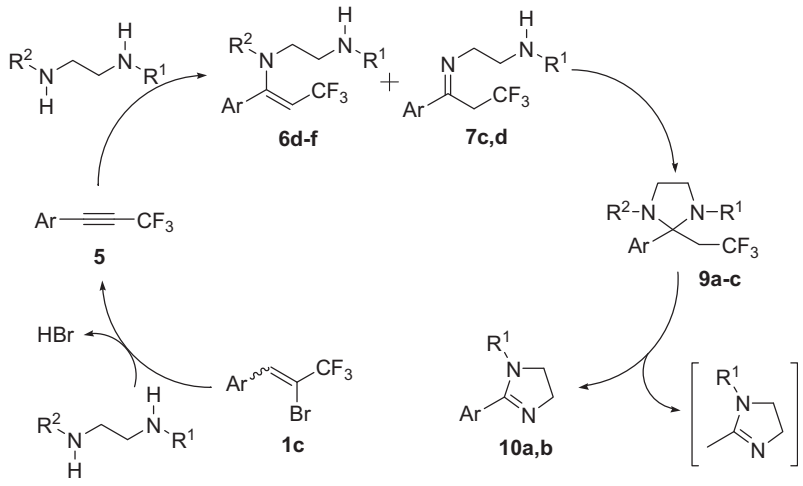

**Scheme 5.** The reactions of amines with EDG-substituted styrenes. **6**,**8**: $NR_1R_2 = N(CH_2)_4$ (**a**), $NHPr^i$ (**b**), NHCy (**c**); **7**: $R_1 = Pr^i$ (**a**), Cy (**b**).

After some minutes of mixing the doublet at −48.4 ppm ($^3J$(F,H) = 7.9 Hz) was appeared in $^{19}F$ NMR spectra. NMR data (1D ($^1H$, $^{13}C$, $^{19}F$)) of this intermediate are in good agreement to those previously reported for the enamine **6a**, which was the product of amine addition to acetylene **5** [6]. 2D NMR (HMBC, NOESY) experiments confirmed additionally the structure of enamine **6a**. The simultaneous increasing of its intensity and decreasing of intensity of **5** was observed during further progress of the reaction (Fig. 2). The intermediate **6a** undergoes further transformations as we described previously to form salts **8a** [6].

Therefore, alkenes bearing EDG react in alternative pathway *via* an elimination–addition sequence. This conclusion was made after the study of the reaction of styrene **1c** with both primary and secondary amines as well as diamines (see Supporting Information, Sections 2.1 and 2.2). Scheme 5 shows the stepwise reaction between styrene **1c** and nitrogen nucleophiles, including the proposed principal intermediates **5**–**7**. The results obtained suggest a stepwise mechanism (E–Ad) including the formation of acetylenic derivative **5** as a key intermediate.

Finally, all principal intermediates were also registered in the reaction of styrene **1c** with binucleophiles. For detecting intermediates, the reactions were monitored with excess of ethylenediamine or its N-methyl- or N,N′-dimethyl substituted derivatives at room temperature without any solvent. Under these conditions, acetylene **5** was formed almost exclusively for the first 5 min of reaction of styrene **1c** with ethylenediamine. In some minutes, the intensity of the signal at −48.9 ppm (acetylene **5**) has begun to decrease and three new low-intensity signals (ca. 5–15%) have appeared. Judging by their multiplicity and chemical shift values, a doublet at −46.6 ppm ($^3J$ (F,H) = 7.6 Hz) was assigned to enamine **6d** and two triplets at −60.7 and −62.2 ($^3J$ (F,H) = 10.7 Hz) were attributed to its azomethine isomer **7c** (Scheme 6). Then, a new triplet at −60.1 ppm ($^3J$ (F,H) = 11.4 Hz) has appeared which was attributed to imidazolidine **9a**. Notice that the reaction of binucleophiles with styrene **1c** occurred as anti-addition process leading to the formation of only one of two possible geometric isomers of the enamine **6d**: no other signal of this derivative has been detected in $^{19}F$ NMR spectra. After 1 h of the reaction the singlet of acetylene **5** was disappeared completely, the intensities of all multiplets have begun to decrease and finally the signal of fluoride anion has appeared due to the fragmentation of the products of substitution of all fluorine atoms of $CF_3$ group.

In principle, it is possible to imagine more complex situation when the electronic influence of the substituents in benzene ring for styrenes **1** is intermediate between 4-nitro and 4-methoxy groups. In this case both mechanisms of substitution could be observed. In fact, the reaction of 4-chloro substituted styrene **1d** with ethylenediamine really gave both types of the products [8].




**Scheme 6.** The reactions of binucleophiles with EDG-substituted styrenes. **6**: $R_1 = R_2 = H$ (**d**); $R_1$ = Me, $R_2$ = H (**e**); $R_1 = R_2$ = Me (**f**); **7**: $R_1$ = H (**c**), $R_1$ = Me (**d**); **9**: $R_1 = R_2 = H$ (**a**); $R_1$ = Me, $R_2$ = H (**b**); $R_1 = R_2$ = Me (**c**); and **10**: $R_1$ = H (**a**), $R_1$ = Me (**b**).

It means that the imidazolidine type **4** is formed through addition–elimination sequence but the corresponding imidazoline type **10** is a result of the competitive elimination–addition pathway.

## 3. Conclusions

The mechanism of the reaction of trifluoromethylated styrenes **1** with amines was studied. We found that the nature of the principle intermediates and the sequence of reaction steps involving in adduct (Ad–E) or alkyne derivative formation (E–Ad) were elucidated. Providing the direct evidence for two different multistep mechanisms of nucleophilic vinylic substitution of halostyrenes **1**, this investigation allowed the understanding of influence of the nature of aromatic substituent on the course of their reaction with nitrogen nucleophiles. It was unambiguously determined that the acetylene **5** and enamine **6** are the key intermediates in the synthesis of vinylogous amidinium salts (primary and secondary amines) or imidazolines (diamines). In contrast, nucleophilic substitution in EWG styrenes occurs *via* addition–elimination sequence. Thus, the substituent in aromatic moiety is an original switch of the reaction direction.

## 4. Experimental

### 4.1. General remarks

$^{19}F$ (376.5 MHz), $^{1}H$ (400.1 MHz), $^{13}C$ (101.6 MHz) NMR spectra were recorded on Bruker AVANCE 400 MHz spectrometers for solutions in MeOH or without it (in excess of amine). Chemical shifts ($\delta$) in ppm are reported using a capillary with chloroform-*d* (7.25 for $^{1}H$) and trifluoroacetic acid (−76.0 for $^{19}F$) as external references. The coupling constants (*J*) are given in Hertz. The concerted application of $^{1}H$–$^{1}H$ 2D homonuclear experiments COSY [13] and NOESY [14] as well as $^{1}H$–$^{13}C$ 2D heteronuclear experiments HSQC [15] and HMBC [16] were used for the distinction of the carbon and proton resonances. The silica gel used for flash chromatography was 230–400 Mesh. All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and freshly distilled prior to use.

β-Fluoro-, β-chloro- and β-bromo-β-trifluoromethylstyrenes **1a–c** were prepared as reported previously [17]. All calculations were performed for gas phase at MP2/6-311+G(d,p) level using Firefly QC package [18], which is partially based on the GAMESS (US) [19] source code.

The NMR tubes (5 mm) were used for the monitoring of the reactions. The amount of each species was determined by integration of the corresponding fluorine signal (with an error of ±1%). A solution of styrene **1** (0.1–0.4 mmol) and amine (or diamine) (0.6–4.0 mmol) in MeOH (or without solvent) was prepared and added to NMR tube. The $^{19}F$ NMR spectra were detected immediately after mixing. The time of each experiment depended on the reaction rate. The spectra obtained were analyzed in comparison with the spectra of pure compounds.

### 4.2. Reaction of β-fluoro-β-trifluoromethylstyrene 1b with pyrrolidine

The mixture of styrene **1b** (82 mg, 0.35 mmol) and pyrrolidine (225 mg, 3.5 mmol) in methanol was allowed to stay at room temperature. When the reaction was completed (control by $^{19}F$ NMR), the enamine **2a** was isolated by column chromatography (Silica gel, $CHCl_3$/methanol (95:5)); yield 96 mg (96%). The NMR spectra of enamine obtained were similar to ones described previoulsy [6].

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at.doi:10.1016/j.jfluchem.2011.07.015

## References

[1] For the fundamental reviews, see:
(a) C.F. Bernasconi, Z. Rappoport, Acc. Chem. Res. 42 (2009) 993–1003;
(b) Z. Rappoport, Recl. Trav. Chim. Pays-Bas 104 (1985) 309–349;
(c) Z. Rappoport, Acc. Chem. Res. 14 (1981) 7–15;
(d) T. Okuyama, G. Lodder, Adv. Phys. Org. Chem. 37 (2002) 1–56;
(e) D. Cohen, R. Bar, S.S. Shaik, J. Am. Chem. Soc. 108 (1986) 231–240;
(f) B.A. Shainyan, Russ. Chem. Rev. 55 (1986) 511–530;
(g) G. Modena, Acc. Chem. Res. 4 (1971) 73–80.
[2] For reviews, see:
(a) A.Yu. Rulev, Usp. Khim. 67 (1998) 317–332;
Russ. Chem. Rev. 67 (1998) 279–293;
(b) A.Yu. Rulev, Usp. Khim. 71 (2002) 225–254;
Russ. Chem. Rev. 71 (2002) 195–221.
[3] (a) A.Yu. Rulev, J. Maddaluno, J. Phys. Org. Chem. 15 (2002) 590–598;
(b) A.Yu. Rulev, S.V. Fedorov, Yu.A. Chuvashov, M.G. Voronkov, Zh. Org. Khim. 39 (2003) 691–694;
(c) A.Yu. Rulev, I.A. Ushakov, V.G. Nenajdenko, E.S. Balenkova, M.G. Voronkov, Eur. J. Org. Chem. (2007) 6039–6045;
(d) A.Yu. Rulev, I.A. Ushakov, V.G. Nenajdenko, Tetrahedron 64 (2008) 8073–8077.

[4] (a) W. Dmowski, J. Fluorine Chem. 26 (1984) 379–394;
(b) J.P. Bégué, D. Bonnet-Delpon, D. Bouvet, M.H. Rock, J. Chem. Soc. Perkin Trans. 1 (1998) 1797–1800;
(c) B. Jiang, F. Zhang, W. Xiong, Tetrahedron 58 (2002) 261–264;
(d) V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, G. Haufe, V.G. Nenajdenko, Russ. Chem. Bull. 57 (2008) 2217–2219;
(e) V.M. Muzalevskiy, V.G. Nenajdenko, A.V. Shastin, E.S. Balenkova, G. Haufe, Tetrahedron 65 (2009) 7553–7561;
(f) A.Yu. Rulev, I.A. Ushakov, J. Fluorine Chem. 131 (2010) 53–58;
(g) N.N. Chipanina, T.N. Aksamentova, B.A. Shainyan, A.Yu. Rulev, J. Mol. Struct. (THEOCHEM) 947 (2010) 22–31.

[5] For the recent reviews, see:
(a) P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, Wiley-VCH, Weinheim, 2004;
(b) M. Schlosser, Angew. Chem. Int. Ed. 45 (2006) 5432–5446;
(c) Fluorinated heterocycles, in: A.A. Gakh, K.L. Kirk (Eds.), ACS Symposium Series 1043, Oxford University Press, New York, 2009.
(d) V. Petrov (Ed.), Fluorinated Heterocyclic Compounds. Synthesis, Chemistry and Applications, John Wiley & Sons, New York, 2009;
(e) V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, G. Haufe, V.G. Nenajdenko, Synthesis (2009) 3905–3929;
(f) V.G. Nenajdenko, A.L. Krasovskiy, E.S. Balenkova, Tetrahedron 63 (2007) 12481–12539;
(g) S.V. Druzhinin, E.S. Balenkova, V.G. Nenajdenko, Tetrahedron 63 (2007) 7753–7808.

[6] V.M. Muzalevskiy, V.G. Nenajdenko, A.Yu. Rulev, I.A. Ushakov, G.V. Romanenko, A.V. Shastin, E.S. Balenkova, G. Haufe, Tetrahedron 65 (2009) 6991–7000.

[7] A.Yu. Rulev, V.M. Muzalevskiy, E.V. Kondrashov, I.A. Ushakov, A.V. Shastin, E.S. Balenkova, G. Haufe, V.G. Nenajdenko, Eur. J. Org. Chem. (2010) 300–310.

[8] V.G. Nenajdenko, V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, E.V. Kondrashov, I.A. Ushakov, A.Yu. Rulev, J. Org. Chem. 75 (2010) 5679–5688.

[9] (a) J.E. Huhee, J. Phys. Chem. 70 (1966) 2086–2092;
(b) W. Adcock, A.N. Abeywickrema, J. Org. Chem. 47 (1982) 2957–2966;
(c) R.W. Taft, J. Phys. Chem. 64 (1960) 1805–1815;
(d) S. Chandra, Tetrahedron 22 (1966) 3403–3407.

[10] For the recent review on aza-Michael and *anti*-aza-Michael reaction, see:
A.Yu. Rulev, Usp. Khim. 80 (2011) 211–233;
A.Yu. Rulev, Russ. Chem. Rev. 80 (2011) 197–218.

[11] A.Yu. Rulev, A.S. Mokov, L.B. Krivdin, N.A. Keiko, M.G. Voronkov, Magn. Reson. Chem. 35 (1997) 533–537, and references therein.

[12] V.M. Muzalevskiy, V.G. Nenajdenko, A.V. Shatin, E.S. Balenkova, G. Haufe, Synthesis (2009) 2249–2259.

[13] K. Nagayama, A. Kumar, K. Wüthrich, R.R. Ernst, J. Magn. Reson. 40 (1980) 321–334.

[14] J. Jeener, B.H. Meier, P. Bachmann, R.R. Ernst, J. Chem. Phys. 71 (1979) 4546–4553.

[15] A. Bax, S. Subramanian, J. Magn. Reson. 67 (1986) 565–569.

[16] A. Bax, M.F. Summers, J. Am. Chem. Soc. 108 (1986) 2093–2094.

[17] (a) A.A. Goldberg, V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, V.G. Nenajdenko, J. Fluorine Chem. 131 (2010) 384–388;
(b) V.N. Korotchenko, A.V. Shastin, V.G. Nenajdenko, E.S. Balenkova, Tetrahedron 57 (2001) 7519–7527;
(c) V.G. Nenajdenko, G.N. Varseev, A.V. Shastin, E.S. Balenkova, J. Fluorine Chem. 126 (2005) 907–913;
(d) V.G. Nenajdenko, V.N. Korotchenko, A.V. Shastin, E.S. Balenkova, Russ. Chem. Bull. 53 (2004) 1034–1064.

[18] A. Granovsky, Firefly Version 7.1.G, http://classic.chem.msu.su/gran/firefly/index.html.

[19] M.W. Schmidt, K.K. Baldridge, J.A. Boatz, S.T. Elbert, M.S. Gordon, J.H. Jensen, S. Koseki, N. Matsunaga, K.A. Nguyen, S. Su, T.L. Windus, M. Dupuis, J.A. Montgomery, J. Comput. Chem. 14 (1993) 1347–1363.